REMARKS

Claims 2-19 are pending and under consideration. With this Amendment, pending Claims 2-19 and withdrawn Claims 20-26 and 30-65 are being cancelled, without prejudice against their reintroduction into this or one or more timely filed continuation, divisional or continuation-in-part applications. Claims 66-83 are newly added. Thus, after entry of this Amendment, Claims 66-83 are pending and under consideration. The amendments to the claims, and the various rejections raised in the Office Action are discussed in more detail, below.

Amendments to the Claims

For clarity, Claims 2-19 have been cancelled and replaced with new Claims 66-83. Support for new Claim 66 can be found, for example, in cancelled Claims 4 and 11, and in paragraphs 146-149. Support for new Claim 67 can be found, for example, in cancelled Claim 2. Support for new Claim 68 can be found, for example, in cancelled Claim 3. Support for new Claim 69 can be found, for example, in paragraph 125 in the specification as filed and in Example 4. Support for new Claim 70 can be found, for example, in cancelled Claim 5. Support for new Claim 71 can be found, for example, in cancelled Claim 6. Support for new Claim 72 can be found, for example, in cancelled Claim 7. Support for new Claim 73 can be found, for example, in cancelled Claim 8. Support for new Claim 74 can be found, for example, in cancelled Claim 9. Support for new Claim 75 can be found, for example, in cancelled Claim 10. Support for new Claim 76 can be found, for example in cancelled Claim 12. Support for new Claim 77 can be found, for example, in cancelled Claim 13. Support for new Claim 78 can be found, for example, in cancelled Claim 14. Support for new Claim 79 can be found, for example, in cancelled Claim 15. Support for new Claim 80 can be found, for example, in cancelled Claim 16. Support for new Claim 81 can be found, for example, in cancelled Claim 17. Support for new Claim 82 can be found, for example, in cancelled Claim 18. Support for new Claim 83 can be found, for example, in cancelled Claim 19.

No new matter is added by virtue of the amendments.

Rejection Under 35 U.S.C. § 103 (a)

The Patent Office has made the following rejections under 35 U.S.C. § 103(a):

Claims 4-19 are rejected as being unpatentable over Cheo *et al.*, U.S. Patent Application Publication No. 2002/0007051 ("Cheo *et al.*") in view of Seibler *et al.*, 1997, Biochemistry, 36:1740-1747 ("Seibler *et al.*");

Claims 4-19 are rejected as being unpatentable over Cheo *et al.*, U.S. Patent Application Publication No. 2002/0007051 ("Cheo *et al.*") in view of Cox *et al.*, U.S. Patent No. 6,140,129 ("Cox *et al.*"); and,

Claims 2-5, 8, 11, 14 and 19 are rejected as being unpatentable over Ow, U.S. Patent Application Publication No. 2002/0123145 ("Ow") in view of Schlake *et al.*, 1994, Biochemistry, 33:12746-12751 ("Schlake *et al.*").

The rejections are moot as applied to cancelled Claims 2-19. Applicant traverses the rejections as they apply to new Claims 66-83.

A. Criteria for Establishing a Prima Facie Case of Obviousness

Section 103(a) precludes the grant of a patent only if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." 35 U.S.C. § 103(a). The Patent Office bears the initial burden of establishing a case of *prima facie* obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1998); MPEP § 2142.

To establish a proper *prima facie* case, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation that the modification or combination would be successful. Finally, the prior art reference (or references when combined) must teach

all the limitations of the rejected claims. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based upon Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), citing *In re Dow*, 5 USPQ2d 1529 (Fed. Cir. 1988); MPEP § 2142.

B. The combination of Cheo *et al.* and Seibler *et al.* fails to teach or suggest all of the limitations recited in new Claims 66-83

New Claims 66–83 recite a first and a second integration cassette capable of stable and random insertion into a discrete genomic position comprising, among other things, an exchangeable reporter segment comprising a scorable homeostatic reporter element, which comprises at least one scorable reporter gene. As set forth in the specification at ¶ 125, cells containing a scorable reporter can be isolated without placing the cells under selective pressure, *e.g.*, drug selection, or otherwise risking cell viability, such as lysing the cells to obtain extracts for the quantification of enzyme activity.

As noted by the Patent Office, Cheo *et al.* teach compositions comprising vectors having multiple recombination sites which permit the joining or combining two or more segments or molecules of nucleic acid by a recombination reaction between recombination sites. Additionally, the vectors taught by Cheo *et al.* can include primer sites, promoters or enhancers, ribosomal binding sites, Kozak sequences, start codons, stop codons, origins of replication, selectable markers, and genes or portions of genes that can be used to create protein fusions (see, e.g., ¶ 50 and). The vectors can be inserted into a host cell where they can replicate autonomously or integrate into one or more nucleic acid molecules that normally reside in the host cell by site-specific recombination or homologous recombination (see ¶ 330). The vectors of Cheo *et al.* do not include a scorable homeostatic reporter element comprising at least one scorable reporter gene, nor are they capable of random insertion into a discrete genomic position in a host cell.

Seibler *et al.*, teach expression cassettes, comprising a set of FRTs, a reporter and a selectable marker (see, page 1743). The reporter taught by Seibler *et al.*, is luciferase, which is

detected by assaying extracts obtained from lysed cells (see, page 1741). As noted by the Patent Office, FLP is provided on a separate vector. Seibler *et al.* do not teach expression cassettes comprising a scorable homeostatic reporter gene.

At a minimum, the combination of Cheo *et al.* and Seibler *et al.* fails to teach or suggest all of the limitations recited in new Claims 66-83. Specifically, the combination of Cheo *et al.* and Seibler *et al.* fails to teach or suggest an integration cassette comprising an exchangeable reporter segment comprising a scorable homeostatic reporter element comprising at least one scorable reporter gene, which is capable of stable and random insertion into a discrete genomic position in a host cell. Accordingly, the Patent Office has not established a *prima facie* case of obviousness. Applicant respectfully submits that new Claims 66-83 are patentable over Cheo *et al.* in view of Seibler *et al.*; thus, a rejection of new Claims 66-83 under 35 U.S.C. § 103(a) would be in error.

C. The combination of Cheo *et al.* and Cox *et al.* fails to teach or suggest all of the limitations recited in new Claims 66-83

New Claims 66-83 have been summarized above.

The teaching of Cheo *et al.* has been discussed above.

As noted by the Patent Office, Cox *et al.* teach that FLP recombinase activity can be provided in a host cell through the regulated expression of its gene on a plasmid. However, there is no teaching in Cox *et al.* of integration vectors comprising at least one scorable homeostatic reporter element comprising at least one scorable reporter gene. Thus, the combination of Cheo *et al.* and Cox *et al.* fails to teach or suggest all of the limitations recited in new Claims 66-83. Specifically, the combination of Cheo *et al.* and Cox *et al.* fails to teach or suggest an integration cassette comprising an exchangeable reporter segment comprising a scorable homeostatic reporter element comprising at least one scorable reporter gene, which is capable of stable and random insertion into a discrete genomic position in a host cell. Accordingly, the Patent Office has not established a *prima facie* case of obviousness. Applicant respectfully submits that new

Claims 66-83 are patentable over Cheo *et al.* in view of Cox *et al.*; thus, a rejection of new Claims 66-83 under 35 U.S.C. § 103(a) would be in error.

D. The combination of Ow and Schlake *et al.* fails to teach or suggest all of the limitations recited in new Claims 66-83

New Claims 66-83 have been summarized above.

The Patent Office states that Ow teaches "a first integration cassette (receptor construct) comprising a promoter operably linked to a first exchangeable reporter segment comprising a thymidine kinase (tk) coding region (scorable homeostatic reporter element) and a zeocin resistance coding region (exchangeable reporter gene), wherein the tk coding sequence is linked to a first recombinase recognition site (PP') at its 5' end and to a second recombinase recognition site at its 3'end (PP") (e.g. Figure 4)".

Applicant respectfully points out the Patent Office has mischaracterized the teaching of Ow, as illustrated in Figure 4 and described in Example 2. As described in Example 2, the target construct illustrated in Figure 4 includes the PS-zeo fragment and the tk gene. The Ps-zeo fragment permits selection of the target construct in the host genome, and the tk gene is a counter-selectable marker. Under appropriate culture conditions, cells that have lost the tk gene will thrive, while those retaining the tk gene will not (see, e.g., ¶ 120). Thus, the various construct embodiments taught by Ow teaches the use of selectable markers, not scorable markers, as recited in new Claims 66-83.

Schlake *et al.* teach expression cassettes using the FLP/FRT system for site specific recombination, which include hygromycin for positive selection and gancyclovir for negative selection (see page 12746). FLP recombinase acitivity is provided using a FLP recombinase plasmid (see page 12747). Schlake *et al.* do not teach expression cassettes comprising at least one scorable homeostatic reporter element comprising at least one scorable reporter gene.

Thus, the combination of Ow and Schlake *et al.* fails to teach or suggest all of the limitations recited in new Claims 66-83. Specifically, the combination of Ow and Schlake *et al.* fails to teach or suggest an integration cassette comprising an exchangeable reporter segment comprising a scorable homeostatic reporter element comprising at least one scorable reporter gene, which is capable of stable and random insertion into a discrete genomic position in a host cell. Accordingly, the Patent Office has not established a *prima facie* case of obviousness. Applicant respectfully submits that new Claims 66-83 are patentable over Ow in view of Schlake *et al.*; thus, a rejection of new Claims 66-83 under 35 U.S.C. § 103(a) would be in error.

Conclusion

Claims 66-83 are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly requested.

No fees beyond those submitted herewith are believed to be due in connection with this Amendment. However, the Commissioner is authorized to charge any additional fees that may be required, or credit any overpayment, to PDL BioPharma, Inc., Deposit Account No. 50-3270 **(Docket No. 118 US UT01)**.

Respectfully submitted,

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